The Role of the Terminal Nerve and GnRH in Olfactory System Neuromodulation

Authors: Kawai, Takafumi, Oka, Yoshitaka, and Eisthen, Heather

Source: Zoological Science, 26(10) : 669-680

Published By: Zoological Society of Japan

URL: https://doi.org/10.2108/zsj.26.669

ZOOLOGICAL SCIENCE **26**: 669–680 (2009)

[REVIEW]

The Role of the Terminal Nerve and GnRH in Olfactory System Neuromodulation

Takafumi Kawai[1], Yoshitaka Oka[1] and Heather Eisthen[2]*

[1]*Department of Biological Sciences, Graduate School of Science, The University of Tokyo, Bunkyo-ku, Tokyo 113-0033, Japan*
[2]*Department of Zoology, Michigan State University, East Lansing, Michigan 48824, USA*

Animals must regulate their sensory responsiveness appropriately with respect to their internal and external environments, which is accomplished in part via centrifugal modulatory pathways. In the olfactory sensory system, responsiveness is regulated by neuromodulators released from centrifugal fibers into the olfactory epithelium and bulb. Among the modulators known to modulate neural activity of the olfactory system, one of the best understood is gonadotropin-releasing hormone (GnRH). This is because GnRH derives mainly from the terminal nerve (TN), and the TN-GnRH system has been suggested to function as a neuromodulator in wide areas of the brain, including the olfactory bulb. In the present article we examine the modulatory roles of the TN and GnRH in the olfactory epithelium and bulb as a model for understanding the ways in which olfactory responses can be tuned to the internal and external environments.

Key words: GnRH, terminal nerve, neuromodulation, olfactory epithelium, olfactory bulb

INTRODUCTION

Animals receive important information about their environment via their sensory organs, enabling organisms to respond appropriately to external cues. The olfactory system plays an important role in translating environmental chemical information into electrical signals that can be recognized accurately. In this system, odorant information is first received by olfactory receptor neurons in the olfactory epithelium. Olfactory bulbar neural circuits then process this information and transmit it to other regions of the central nervous system. To maximize efficiency, an animal should regulate its responsiveness to olfactory information depending on its physiological condition, such as its nutritional or reproductive state.

Centrifugal modulation is widespread among vertebrate sensory organs, functioning to tune sensory responses with respect to both the internal and external environments. For example, in reptiles, birds, and mammals, innervation of cochlear outer hair cells can enhance sensitivity and frequency selectivity (Nobili et al., 1998; Manley, 2000, 2001). This innervation can depress activity to prevent noise-induced damage, and can enhance the signal-to-noise ratio in a moderately noisy background (Rajan, 2000; Christopher Kirk and Smith, 2003). Cochlear physiology can also be altered by signals arising internally. For example, electrical stimulation in the primary auditory cortex of mustached bats (*Pteronotus parnellii*) changes frequency tuning in the cochlea (Xiao and Suga, 2002), and focused visual or auditory attention modulates otoacoustic emissions in humans (Puel et al., 1988; Maison et al., 2001). In midshipman fish (*Porichthys notatus*), centrifugal modulation preserves sensitivity to externally generated sounds during vocalization (Weeg et al., 2005). Thus, in the auditory system, centrifugal innervation functions to preserve sensitivity and to highlight important stimuli. Similar phenomena may occur in the olfactory system, although they have not been the subject of systematic investigation. Nevertheless, a few examples emerge from studies in a range of vertebrates. For example, when rats are food deprived, centrifugal pathways produce selective facilitation or disinhibition of olfactory bulbar responses to food odorants (Pager et al., 1972; Pager, 1978), suggesting that in the olfactory system, as in the auditory system, modulation of sensory responses may enable animals to respond optimally to sensory stimuli.

Here, we will review the available literature concerning the centrifugal modulation of olfactory sensitivity, focusing on the peptide gonadotropin-releasing hormone (GnRH), which is the best-studied neuromodulator in the olfactory system. In some teleost fishes, different GnRH systems in the brain express specific forms of the GnRH peptide (reviewed in Okubo and Nagahama, 2008). Studies using immunocytochemical methods to identify the source of the form of GnRH present in the olfactory epithelium and bulb in teleost fishes have shown that the terminal nerve (TN) is

* Corresponding author. Phone: +1-517-353-1953;
Fax : +1-517-432-2789;
E-mail: eisthen@msu.edu
doi:10.2108/zsj.26.669

the major source of GnRH to these areas (Yamamoto et al., 1995; Amano et al., 2002); Fig. 1 illustrates the innervation of olfactory areas by GnRH-immunoreactive fibers in a goldfish (*Carassius auratus*). The TN is likely also main source of the GnRH-immunoreactive fibers distributed throughout the olfactory system in amphibians and mammals (Wirsig and Getchell, 1986; Wirsig and Leonard, 1986b).

The TN was the last macroscopically identifiable cranial nerve to be discovered, and was first described in elasmobranchs (Fritsch, 1878; Locy, 1905). In many vertebrates, one or more TN ganglia are located near or within the olfactory nerve, olfactory bulb, or ventral telencephalon; these cells contain GnRH as well as other neurotransmitters and neuromodulators. Lesion experiments suggest that the TN is involved in the control of the motivational state of the animal (Wirsig, 1987; Yamamoto et al., 1997). For example, in the dwarf gourami (*Colisa lalia*), a model animal for studies of the TN, lesions of the TN in males result in a decrease in motivation for the nest-building behavior, an important component of male reproductive behavior (Yamamoto et al., 1997). Because GnRH neurons receive direct and indirect inputs from the somatosensory, visual, and olfactory systems (Yamamoto and Ito, 2000), these neurons probably respond to changes in the animal's environment; these pathways are illustrated in Fig. 2. TN neurons may then regulate olfactory responses accordingly by releasing GnRH or other chemical substances into the olfactory epithelium, bulb, or both.

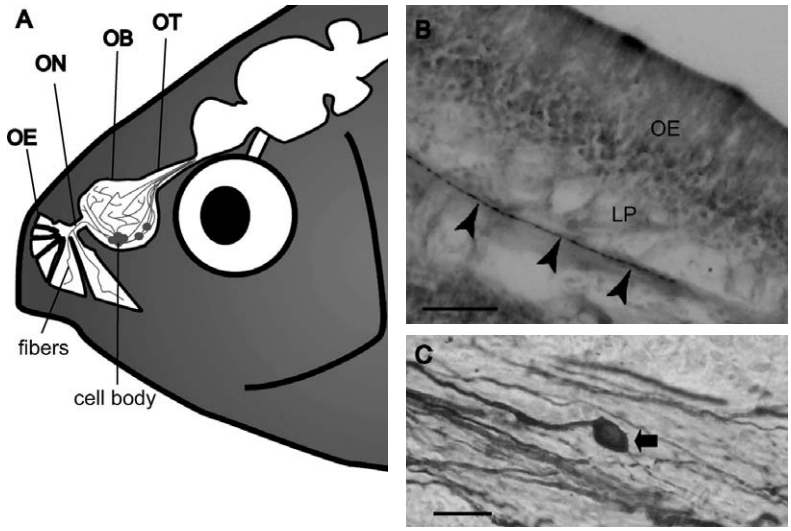

Fig. 1. GnRH-immunoreactive fibers in the olfactory epithelium and bulb of a goldfish (*Carassius auratus*). **(A)** Schematic illustration of TN-GnRH cell bodies and fibers in the olfactory system of the goldfish. For clarity, the position of the brain is illustrated dorsal to the eye and the sizes of the olfactory epithelium and bulb are magnified. In the goldfish, the TN ganglion cells are located in the transitional area between the olfactory nerve and the olfactory bulb, from which they extend fibers to the olfactory epithelium and bulb. Additional GnRH-immunoreactive fibers, not shown here, run through the medial olfactory tract and extend principally to areas of the telencephalon, optic tectum, dorsal thalamus, and spinal cord as well as through the optic nerve to the retina. LP, lamina propria; OB, olfactory bulb; OE, olfactory epithelium; ON, olfactory nerve; OT, olfactory tract. **(B)** Photomicrograph of GnRH immunoreactive fibers (arrowheads) underneath the olfactory epithelium of a goldfish. Scale bar, 50 μm. **(C)** Photomicrograph of a GnRH immunoreactive cell body (arrow) and fibers in the olfactory bulb of a goldfish. Scale bar, 50 μm.

In the present article, we will describe the modulatory effects of peptidergic neuromodulators on the olfactory system, focusing on the role of the TN and GnRH. Because most studies of the modulatory effects of GnRH on the olfactory system involve teleost fishes and salamanders, we will mainly focus on these groups. We will discuss the effects on the olfactory epithelium and bulb separately.

MODULATION IN THE OLFACTORY EPITHELIUM

Organization of the olfactory epithelium

The pseudostratified olfactory sensory epithelium is organized similarly in all vertebrates (reviewed in Eisthen and Polese, 2006). The most superficial somata belong to the sustentacular cells, a class of secretory supporting cells. The somata of the olfactory receptor cells lie below those of the sustentacular cells, and the deepest layer contains the basal cells, which serve as progenitors for the olfactory receptor and sustentacular cells. The surface of the olfactory epithelium is bathed in specialized mucus, which is largely produced by nasal glands adjacent to the olfactory epithelium, as well as by Bowman's glands, which lie deep to the olfactory epithelium. The secretory activity of the sustentacular cells also contributes to this fluid.

Olfactory receptor cells are unusual among vertebrate sensory cells in that they are primary neurons, rather than modified epithelial cells. The unmyelinated axons of these

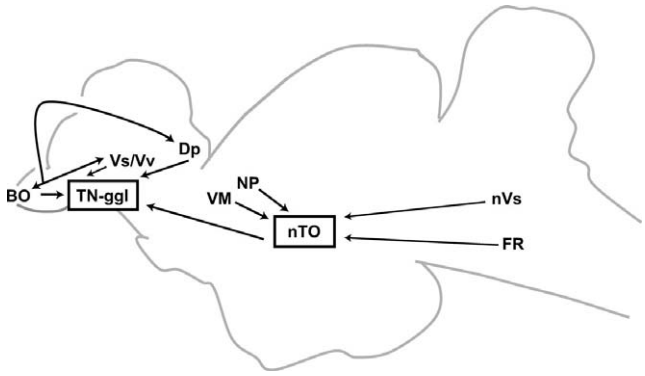

Fig. 2. Schematic illustration of the afferent sources to the TN ganglion in teleost fishes, as described by Yamamoto and Ito (2000). For clarity, the relevant regions are shown in their approximate positions in a side view of the brain of a dwarf gourami, *Colisa lalia*, a teleost fish; anterior is to the left and dorsal is up. Large neurons of this ganglion are GnRH-immunoreactive. The TN ganglion receives input from olfactory areas in the forebrain (Vv and Vs) as well as from the nucleus tegmento-olfactorius (nTO, also called the nucleus tegmento-terminalis). Because the nucleus appears to relay somatosensory and visual information, the TN ganglion probably receives multimodal sensory inputs. BO, bulbus olfactorius; Dp, area dorsalis telencephali pars posterior; FR, formatio reticularis; NP, nucleus pretectalis; nVs, nucleus sensorius nervi trigemini; TN-ggl, ganglion of the nervus terminalis; VM, nucleus ventromedialis thalami; Vs, area ventralis telencephali pars supracommissuralis; Vv, area ventralis telencephali pars ventralis.

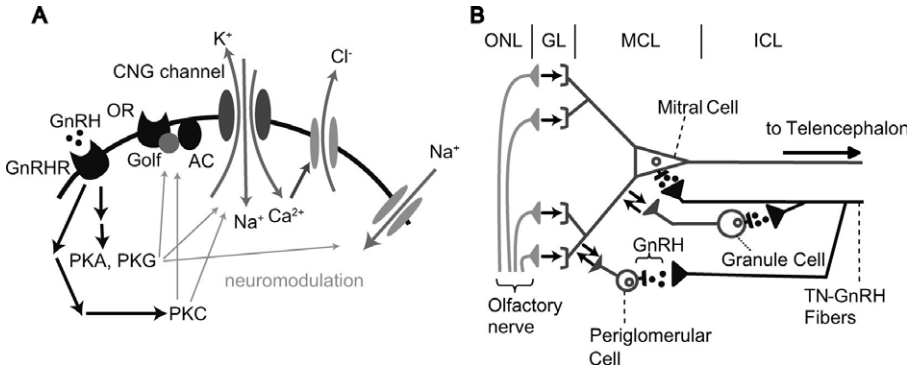

Fig. 3. Possible mechanisms of modulatory effects of GnRH on the olfactory receptor neurons or olfactory bulbar circuits. **(A)** Schematic transduction mechanism in olfactory receptor neurons that express ORs. Odorant binding to ciliary ORs activates adenylyl cyclase via a G protein, opening cyclic nucleotide-gated cation channels. The calcium that flows in then secondarily activates calcium-activated chloride channels, depolarizing the ciliary membrane. In many cases, this stimulates voltage-activated sodium channels. GnRH may modulate these processes through phosphorylation via PKA-, PKG-, or PKC-mediated pathways. AC, adenylyl cyclase; CNG channel, cyclic nucleotide-gated cation channel; G_{olf}, olfactory-specific G protein; OR, odorant receptor. **(B)** Schematic illustration of the neural circuit in the olfactory bulb of a generalized teleost fish. In teleosts, unlike mammals, the somata of periglomerular cells are distributed among the mitral cells (Fuller et al., 2006). GnRH may act on one or more types of neurons, thereby modulating the processing of olfactory information. GL, glomerular layer; ICL, internal cell layer; MCL, mitral cell layer; ONL, olfactory nerve layer.

bipolar neurons generally form small bundles that coalesce into an olfactory nerve projecting to the olfactory bulb at the rostral pole of the telencephalon. At the other pole of the cell, the unbranched dendrite extends into the mucus layer lining the olfactory organ. The tip of the dendrite can contain cilia, microvilli, or both, depending on the species (reviewed in Eisthen, 2004). Transduction occurs when an odorant interacts with a receptor at the surface of the ciliary or microvillar membrane. The most prevalent receptors in all vertebrates are members of the large family of odorant receptor (OR) genes (reviewed in Mombaerts, 2004). A second class of olfactory receptors, the transient amino acid receptors (TAARs), was recently found to be expressed in a small proportion of olfactory receptor neurons, and appears to be widely distributed across vertebrates (Liberles and Buck, 2006). Although it is not yet clear how many TAARs may be expressed in a given cell, individual olfactory receptor cells appear to randomly express only one or only a small subset of OR genes, suggesting the odorant coding may be based in part on the identity of the individual cells that are activated (Ngai et al., 1993; Vassar et al., 1993; Chess et al., 1994; Buck, 2000; Sato et al., 2007).

Finally, members of the two families of vomeronasal receptor genes, the V1Rs and V2Rs, are expressed in the olfactory epithelium in teleost fishes (Cao et al., 1998; Naito et al., 1998; Speca et al., 1999; Saraiva and Korsching, 2007) and in the receptor cells of the vomeronasal organ in amphibians, reptiles, and mammals. Interestingly, members of these two families have also been found to be expressed in small numbers in the olfactory epithelium of frogs (*Xenopus laevis*, Date-Ito et al., 2008), goats (*Capra hircus*, Wakabayashi et al., 2002; Wakabayashi et al., 2007), mice (*Mus musculus*, Karunadasa et al., 2006), and humans (Rodriguez et al., 2000). The phylogenetic diversity of these animals indicates that olfactory epithelial expression of V1R and V2R genes may be widespread among tetrapods, suggesting the existence of four classes of olfactory receptor neurons: those expressing ORs, TAARs, V1Rs, and V2Rs. All four categories of receptors activate G proteins when stimulated. In the majority of olfactory receptor cells, i.e., those expressing ORs, the G protein activates adenylyl cyclase, opening cyclic nucleotide-gated cation channels, which secondarily activate chloride channels. Receptor binding thus leads to an influx of cations and efflux of anions, depolarizing the receptor neuron (Fig. 3A) (reviewed in Schild and Restrepo, 1998, Firestein, 2001).

Sources of GnRH in the olfactory epithelium

The olfactory organ develops from the nasal placode, a thickened disk of tissue that lies anterior to the developing neural plate. The TN ganglion cells also develop from the nasal placode and then migrate centrally during early development, with some cells migrating as far as the hypothalamus (Schwanzel-Fukuda et al., 1985; Schwanzel-Fukuda and Pfaff, 1989; Wray et al., 1989; Hilal et al., 1996; Amano et al., 1998; Amano et al., 2004; Okubo et al., 2006). One or more TN ganglia usually form along the olfactory nerve or ventral olfactory bulb, with fibers that extend rostrally to the olfactory epithelium and caudally to the preoptic area, although collaterals can branch widely throughout the brain (Oka, 1997). The terminals of the rostral processes have proven difficult to locate precisely, but the fibers appear to end in or just underneath the lamina propria that surrounds the olfactory epithelium; additional fibers appear to end near the Bowman's glands (Wirsig-Wiechmann, 1993). Thus, GnRH and other compounds released from TN fibers may diffuse upward through the olfactory epithelium to stimulate cells, or may be released in the mucus overlying the olfactory epithelium, or both.

Although the TN is the only known source of GnRH-containing fibers that project to the olfactory epithelium, in some species other structures associated with the nose are also innervated by GnRH-containing fibers from other sources; for example, in tiger salamanders (*Ambystoma tigrinum*), the palatine ganglion of the trigeminal nerve contains GnRH-immunoreactive fibers that innervate the naris closure muscles (Wirsig-Wiechmann, 1993; Wirsig-Wiechmann and Ebadifar, 2002). In addition, the olfactory epithelium is also well vascularized. Thus, it seems possible that GnRH could reach the cells in the olfactory epithelium from sources other than the TN. Regardless of the mechanism of access or source, GnRH receptors are present in the olfactory epithelium, indicating that GnRH has direct effects on cells in the olfactory epithelium (Wirsig-Wiechmann and Jennes, 1993; Wirsig-Wiechmann and Wiechmann, 2001; Zhang and Delay, 2007). Unfortunately, we do not yet know which specific cell types express which subtypes of GnRH receptor genes.

GnRH immunoreactivity has also been described in primary olfactory receptor neurons in the walking catfish (*Clarias batrachus*; Subhedar and Rama Krishna, 1988) and in the Indian major carp (*Cirrhinus mrigala*; Biju et al., 2003; Biju et al., 2005). In the latter, expression occurs only in young larvae and in adult females, and is seasonal, peaking during the prespawning period (Biju et al., 2003; Biju et al., 2005). In both species, GnRH-immunoreactive olfactory receptor neurons project to glomeruli in the olfactory bulb (Subhedar and Rama Krishna, 1988; Biju et al., 2003; Biju et al., 2005), but it is not known whether these cells release GnRH into the olfactory epithelium, olfactory bulb, or both.

Physiological effects of GnRH in the olfactory epithelium

In axolotls (*Ambystoma mexicanum*), a type of aquatic salamander, GnRH has been shown to modulate responses evoked by amino acids, which act as food cues for aquatic vertebrates (Park and Eisthen, 2003). Specifically, GnRH reduces the magnitude of the odorant response measured using a technique called an electro-olfactogram (EOG) recording that largely reflects a summed generator potential recorded from many olfactory receptor neurons (Scott and Scott-Johnson, 2002). Interestingly, the magnitude of the EOG response rebounds quickly once the GnRH is washed off, and in some cases becomes significantly larger than the initial baseline response (Park and Eisthen, 2003). Although the biological significance of this effect is not yet clear, perhaps GnRH release suppresses responses to food odorants during courtship or breeding, and later promotes an enhanced response to the same odorants to compensate.

The modulatory effect of GnRH on odorant responses has also been measured at the level of individual olfactory receptor neurons in another aquatic salamander, the mudpuppy (*Necturus maculosus*). Zhang and Delay (2007) used either a cocktail of volatile odorants with no inherent behavioral significance for mudpuppies or a mixture of 3-isobutyl-1-methylxanthine (IBMX) and forskolin to stimulate the cAMP-gated odorant transduction pathway. Both stimuli generally suppressed outward currents in olfactory receptor neurons, and GnRH reduced, or counteracted, this suppression. The IBMX+forskolin mixture also elicited an inward current, and the effects of GnRH on this current were variable. The mechanisms by which GnRH alters odorant responses are not known, but the available data suggest that GnRH alters odorant signal transduction. One possible category of mechanisms, phosphorylation of one or more elements of the odorant signal transduction pathway, is illustrated in Fig. 3A.

GnRH does not appear to activate ionic currents directly (Zhang and Delay, 2007), but does modulate the voltage-activated currents in olfactory receptor neurons. Specifically, in isolated mudpuppy olfactory receptor neurons, brief (2- to 3-min) application of GnRH suppresses the tetrodotoxin-sensitive, voltage-activated sodium current in the majority of olfactory receptor neurons; in about half the cells that respond to GnRH, the current is only suppressed for about a minute and then is enhanced for a longer period. These modulatory effects appear to be mediated by PKA and/or PKG, which are activated by one or more cyclic nucleotides (Zhang and Delay, 2007). In separate experiments involving mudpuppy olfactory neurons in epithelial slices, application of GnRH enhanced the magnitude of the same sodium current over a longer time course, 5–40 min (Eisthen et al., 2000). Both studies found varying effects on voltage-activated outward currents, but did not identify the currents involved nor systematically investigate the details of the effects (Eisthen et al., 2000; Zhang and Delay, 2007). Given that the sodium current affected by GnRH likely underlies the action potential in olfactory receptor neurons, these data suggest that GnRH might initially make the cells less excitable, but then in a subset of cells or in the intact epithelium it might make the cell more excitable or more likely to respond to weak stimuli. The effects on voltage-activated and odorant-stimulated outward currents are more complex, and current-clamp recordings during odorant stimulation should be used to measure directly the effects of GnRH on cell excitability and odorant sensitivity.

Both studies that examined effects of GnRH at the single-cell level in mudpuppies found that about twice as many olfactory receptor neurons responded to GnRH during the breeding season compared with the non-breeding season (Eisthen et al., 2000; Zhang and Delay, 2007). Park and Eisthen (2003) only used axolotls in breeding condition, but their data suggest that in such animals GnRH may briefly suppress responses to food odorants. Finally, Propper and Moore (1991) showed that GnRH levels in TN fibers increase during courtship in another salamander, female rough-skinned newts (*Taricha granulosa*). In the central nervous system, GnRH plays a key role in coordinating endocrine activity during vertebrate reproduction; taken together, these results suggest that the GnRH-containing fibers of the TN may also help coordinate sensory responses to olfactory stimuli that are important for reproduction.

The results described above are intriguing, but many questions remain concerning the mechanisms and function of GnRH modulation in the olfactory epithelium. For example, the study by Zhang and Delay (2007) demonstrates that GnRH directly affects at least some olfactory receptor neurons, as the authors recorded from isolated cells. However, we do not know whether GnRH might also influence the other types of cells in the olfactory epithelium, the sustentacular or basal cells, or other nearby tissues such as secretory glands. In addition, it seems possible that GnRH may affect the activity of some cells directly, but may also cause the release of secondary compounds that modulate activity in other cells. Finally, we do not know why GnRH affects the activity of some olfactory receptor neurons but not others. Do the two groups of cells differ in some way? Perhaps GnRH affects the activity of neurons that respond to certain odorants, or classes of odorants, while having no effect on neurons that respond to other odorants. Similarly, it seems possible that GnRH receptors are co-expressed with some types of odorant receptor, or some subcategories of the OR family, but not others. These questions should be resolved by studies using imaging techniques or single-cell RT-PCR.

Other modulatory influences on the olfactory epithelium

In addition to GnRH, the TN contains other potentially modulatory compounds; for example, the TN in most vertebrates is FMRFamide-immunoreactive. Although FMRFamide is a molluscan peptide that is not present in vertebrate brains (Chartrel et al., 2006; Tsutsui and Ukena, 2006), structurally similar molecules (RFamides) are likely to

be present. In goldfish, chromatography and radioimmunoassay data suggest that two RFamides are present in the TN (Fischer et al., 1996). One of these peptides may be an LPXRFamide, a member of a family of peptides that terminate in the sequence LPXRF-NH_2 (where X=L or Q; see Tsutsui and Ukena, 2006, for review). In goldfish, a novel precursor gene encodes three different LPXRFamides, although only one peptide (gfLPXRFa-3) may be produced in the brain and TN (Sawada et al., 2002). The other RFamide may be *Carassius* RFamide (C-RFa, Fujimoto et al., 1998). Although its presence in the goldfish TN has not been demonstrated unequivocally (Satake et al., 1999), the olfactory tract of Atlantic salmon (*Salmo salar*) contains C-RFa immunoreactive fibers, suggesting that the peptide could be produced by TN cells (Montefusco-Siegmund et al., 2006). In addition, some anti-FMRFamide antisera cross-react with NPY, which has a similar C terminal (Chiba et al., 1996; Chiba, 2000), and the TN in some species almost certainly contains NPY (Chiba, 2005; Mousley et al., 2006). Finally, the TN has been reported to contain acetylcholine (ACh), a compound often present in modulatory systems: histochemical and pharmacological data suggest its presence in the TN of tiger salamanders and bonnethead sharks (*Sphyrna tiburo*), as well as that of at least young rats (*Rattus norvegicus*) and chicks (*Gallus domesticus*) (Schwanzel-Fukuda et al., 1986; Wirsig and Leonard, 1986a; Wirsig-Wiechmann, 1990; White and Meredith, 1995). Some reports also suggest that glutamate may serve as a co-transmitter in GnRH-containing neurons (Dumalska et al., 2008).

The relative distribution of TN compounds appears to vary considerably among species. For example, ACh histochemistry and GnRH immunoreactivity distinguish separate populations of fibers in tiger salamanders (Wirsig and Leonard, 1986b), but acetylcholine appears to be present in both RFamide- and GnRH-immunoreactive fibers in bonnetheads (White and Meredith, 1995). Immunoreactivity data from tiger salamanders, bonnetheads, and cloudy dogfish (*Scyliorhinus torazame*) indicate that GnRH and RFamides or NPY are found in separate populations of cells (White and Meredith, 1995; Chiba, 2000; Wirsig-Wiechmann et al., 2002), suggesting that release of these peptides could be regulated independently. In contrast, these peptides appear to co-localize in the TN in teleosts and perhaps in all actinopterygians (Batten et al., 1990; Chiba et al., 1996; Chiba, 1997; Wirsig-Wiechmann and Oka, 2002; Chiba, 2005), suggesting that they are co-released. If so, the effects of GnRH may be modified by simultaneous release of ACh, NPY, or RFamides.

The effects of some of these TN-derived compounds have been studied in the olfactory epithelium. In contrast to GnRH, which suppresses EOG responses evoked by amino acids, NPY enhances the magnitude of responses to the same odorants in axolotls (Mousley et al., 2006). Like GnRH, though, NPY enhances the magnitude, but does not alter the kinetics, of the tetrodotoxin-sensitive sodium current in olfactory receptor neurons in slices of olfactory epithelium from adult axolotls (Mousley et al., 2006). As with GnRH, these effects depend on the physiological state of the animal: the EOG response is enhanced only in food-deprived animals, and the effect on the sodium current occurs in more than three times as many cells in food-deprived animals compared with well-fed animals (Mousley et al., 2006). These results are interesting given that NPY plays an important role in regulating hunger and appetite (see Michel, 2004, for review). Unfortunately, we do not yet know whether these physiological variables interact; for example, perhaps GnRH suppresses responses to food odorants in well-fed animals during the breeding season, but enhances the same responses during the non-breeding season to support later reproduction.

Park and colleagues (2003) examined the effects of FMRFamide on the olfactory epithelium in axolotls, and found that it enhanced the magnitude of the sodium current in olfactory receptor neurons but had no effect on EOG responses elicited by amino acids. A more recent study (Ni et al., 2008) using isolated olfactory receptor neurons from mice demonstrated that FMRFamide enhanced the magnitude of the delayed rectifier potassium current (I_K), but had no effect on the kinetics of the current nor on the magnitude or kinetics of the fast transient potassium current (I_A). The authors conclude that FMRFamide could cause olfactory receptor neurons to repolarize more quickly following an action potential, facilitating odorant responses (Ni et al., 2008). The results of both studies are difficult to interpret, however, in part because FMRFamide is not an endogenous compound in vertebrates, and in part because the authors of these studies did not manipulate the physiological state of the subjects. RFamides may serve a variety of functions (e.g., Chartrel et al., 2006) but seem to play a role in feeding behavior (Dockray, 2004); perhaps FMRFamide would have different effects in food-deprived mice or axolotls compared with the well-fed animals that were used in these experiments. Finally, ACh has been reported to evoke direct excitatory responses from olfactory receptor neurons in frogs (*Rana ridibunda*, Bouvet et al., 1984; Bouvet et al., 1988), but it is not clear whether it also exerts modulatory effects.

Activity in the olfactory epithelium is subject to modulation by compounds from other sources in addition to the TN. In rodents, leptin appears to be synthesized in nasal glands and released into the mucus overlying the olfactory epithelium, where both the receptor neurons and the supporting cells express leptin receptors (Getchell et al., 2006; Baly et al., 2007). In rats, both cell types also express orexins and orexin receptors (Caillol et al., 2003). While these data suggest that orexins and leptin could modulate odorant responses in the olfactory epithelium through paracrine mechanisms, direct evidence of this phenomenon has not yet been published. Finally, a recent paper (Czesnik et al., 2007) demonstrates that endocannabinoids modulate odorant responses in African clawed frogs (*Xenopus laevis*), indicating another mechanism by which hunger could modulate activity in the olfactory epithelium. A physiological source of endocannabinoid release into the olfactory epithelium has not yet been identified. Similarly, both adrenaline and serotonin have been shown to modulate activity in the olfactory epithelium, although a plausible local source for these compounds has not been identified (Arechiga and Alcocer, 1969; Kawai et al., 1999; Wetzel et al., 2001).

In addition to the TN, the trigeminal nerve also modulates the activity of olfactory receptor neurons. Dopamine decreases odorant sensitivity and excitability of olfactory receptor neurons (Hegg and Lucero, 2004). The olfactory epithelium is innervated by dopamine-containing fibers from the superior cervical ganglion (Kawano and Margolis, 1985),

and dopamine levels in the olfactory mucus are elevated following stimulation of the trigeminal nerve (Lucero and Squires, 1998). Thus, dopamine may be released as part of a feedback loop to protect olfactory receptor neurons from the potentially damaging effects of noxious chemicals that stimulate trigeminal fibers (Hegg and Lucero, 2004). The modulation of olfactory receptor cell activity caused by release of substance P and acetylcholine from trigeminal fibers (Bouvet et al., 1987a; Bouvet et al., 1987b, 1988) may serve a similar function. Damaged olfactory receptor neurons release ATP, which reduces odorant sensitivity in adjacent cells, again serving a neuroprotective function (Hegg et al., 2003).

Taken together, the available data clearly indicate that neural activity in the olfactory epithelium is subject to strong modulation, both to protect the neurons from potentially damaging chemicals and to alter responding with respect to the animal's reproductive and nutritional state. We do not yet know how the sources of modulatory influence in the olfactory epithelium interact with each other.

MODULATION IN THE OLFACTORY BULB

In at least some teleosts, the olfactory bulb receives prominent projections of GnRH-containing fibers from the TN (Fig. 1) (Oka and Matsushima, 1993; Kim et al., 1995; Yamamoto et al., 1995), indicating that the neural circuits of the olfactory bulb are major targets of neuromodulation by GnRH in these species. However, to date no published studies have examined the physiological effects of GnRH in the olfactory bulb; the data available at present only allow us to speculate on the possible neuromodulatory functions of GnRH in the olfactory bulb. Nevertheless, studies using immunohistochemical, radioimmunological, and molecular biological techniques establish a foundation for developing hypotheses concerning the potential effects of GnRH and other neuromodulators in the olfactory bulb, and will be discussed here.

Organization of the olfactory bulb

The olfactory bulb is the primary olfactory center, as it is the first relay in the central nervous system to receive direct projections from the olfactory epithelium. It is organized similarly across all vertebrates. In general, the olfactory bulb is composed of morphologically and functionally distinct neuronal types arranged in distinct layers, and these neurons contribute to the processing of olfactory information that is conveyed from the olfactory receptor cells (Fig. 3B) (Shepherd, 2004). First, the olfactory nerve, which consists of bundles of axons of the olfactory receptor neurons, enters the olfactory bulb. These bundles then defasciculate profusely in the superficial part of the olfactory bulb to form synapses in the olfactory "glomeruli", round bundles of neuropil in which the axons of the olfactory receptor neurons interact with dendrites of bulbar neurons. In the glomeruli, axons of olfactory receptor neurons expressing the same odorant receptor genes converge onto one or a few glomeruli in mice and zebrafish (Mombaerts et al., 1996; Sato et al., 2007). Each odorant activates distinct subsets of glomeruli, and thus the olfactory information may be coded in part using patterns of spatial activity (Shepherd, 1994; Friedrich and Korsching, 1997).

In a glomerulus, the axon terminals of olfactory receptor neurons are in contact with the dendrites of mitral cells, the axons of which project out of the olfactory bulb into other olfactory regions in the central nervous system. The mitral cells also form reciprocal dendro-dendritic synapses with granule cells, with cell bodies in the deepest layer of the olfactory bulb and dendrites that extend radially into the mitral cell layer (Rall and Shepherd, 1968). In these reciprocal synapses, the mitral cells form excitatory glutamatergic synapses with the dendrites of granule cells, and the granule cells form GABAergic synapses with the dendrites of the mitral cell. These microcircuits may enhance the tuning specificity of odor responses by lateral inhibition (Rall and Shepherd, 1968; Shepherd and Brayton, 1979; Yokoi et al., 1995).

After odorant information is transmitted from olfactory epithelium to the olfactory bulb, the information is processed through these olfactory bulbar neural circuits, evoking oscillatory activity in the olfactory bulb (Adrian, 1950; Hasegawa et al., 1994; Kashiwadani et al., 1999; Friedrich et al., 2004). Specifically, the mitral cells undergo synchronized subthreshold oscillations in the membrane potential, which are mainly driven by inhibitory inputs of granule cells (Schoppa, 2006). The mitral cells tend to produce action potentials near the peaks of these oscillations in membrane potential, contributing to synchronization of mitral cell action potentials (Friedrich et al., 2004). Although the functional significance of the oscillatory activity in the olfactory system is not thoroughly understood, studies in insects indicate that it is important for odorant discrimination (Stopfer et al., 1997; Laurent et al., 2001).

Through processing in the olfactory bulb, the representation of each odorant by firing in each mitral cell changes continuously. The temporal firing patterning of each mitral cell progressively reduces the similarity between related odors, making the representation of each odorant more specific (Friedrich and Laurent, 2001; Friedrich et al., 2004). Thus, although olfactory information is partially coded by patterns of spatial activity in glomeruli, the temporal patterning of the mitral cell activity is also important in olfactory information processing.

Localization of GnRH fibers and receptors in the olfactory bulb

GnRH-immunoreactive cell bodies and fibers located near or within the olfactory bulb have been described in various vertebrate species, including teleosts (Oka and Ichikawa, 1990; Amano et al., 1991; Kim et al., 1995; Yamamoto et al., 1995; Gonzalez-Martinez et al., 2001; Gonzalez-Martinez et al., 2002), amphibians (D'Aniello et al., 1995), birds (Teruyama and Beck, 2000), and mammals (Kim et al., 1999). In dwarf gourami (*Colisa lalia*), a dense projection of GnRH-immunoreactive fibers extends not only ipsilaterally but also bilaterally from the TN ganglion into the olfactory bulb (Oka and Matsushima, 1993).

The function of GnRH in the olfactory bulb can be inferred from the pattern of projections of GnRH-immunoreactive fibers. GnRH-immunoreactive fibers project to both the mitral and granule cell layers in teleosts (Oka and Matsushima, 1993; Kim et al., 1995). Thus, GnRH probably acts on multiple types of olfactory bulbar neurons, and may modulate the olfactory information processing in a complex fashion. In goldfish, the olfactory bulb is functionally subdivided into a few clearly defined areas. Amino acid odorants, which indicate the presence of food, strongly activate neurons in the lateral region of the olfactory bulb; in contrast, the

neurons of the medial region in the olfactory bulb respond to sex pheromones (Hanson et al., 1998). In spite of this possible functional segregation, projections of GnRH-immunoreactive fibers in the olfactory bulb in goldfish appear to be extensive, and not limited to a certain region (Kim et al., 1995). Thus, GnRH seems to be involved in the modulation on the olfactory bulbar neurons that process different categories of olfactory information. Perhaps GnRH has different effects in different regions, depending on the type of olfactory information being processed.

The mechanisms by which the activity of neural circuits in the olfactory bulb is modulated by GnRH would be clearer if we knew more about the types of olfactory bulbar neurons that express GnRH receptors (Illing et al., 1999). In addition, different subtypes of GnRH receptor may be differentially distributed in the olfactory bulb, as has been reported for various regions of the nervous system in goldfish (Peter et al., 2003). In the retina of a cichlid fish, *Astatotilapia* (*Haplochromis*) *burtoni*, for example, differential distribution of two GnRH receptors has been reported: the type-I receptor is expressed in cells in the amacrine cell layer, while the type-II receptor is expressed in ganglion cells (Grens et al., 2005). Because amacrine cells are involved in processing visual information and ganglion cells relay the processed information to the brain, GnRH would influence each step of this process. Similar information concerning the distribution of GnRH receptors in the olfactory bulb would provide insight concerning the functional role of GnRH in odorant information processing in the olfactory bulb.

Unfortunately, however, few reports describe the distribution of GnRH receptors in the olfactory bulb in detail (Peter et al., 2003; Soga et al., 2005; Albertson et al., 2008). To date, one report indicates that in cichlid fish expression of the GnRHRIII subtype is restricted to the granule cell layer (Soga et al., 2005), and another demonstrates that in mice mitral cells express GnRHRI receptors (Albertson et al., 2008). Clearly, more information concerning the regions and types of neurons that express GnRH receptors, as well as the subtypes of receptors expressed, is needed.

Other modulatory influences within the olfactory bulb

The neuromodulatory effects of some classical neurotransmitters and neuromodulators other than GnRH have been demonstrated in olfactory bulb. These data may provide clues as to the possible neuromodulatory effects of GnRH, and therefore will be summarized here; Fig. 3B illustrates the potential mechanisms discussed below.

First, it is possible that GnRH alters the membrane excitability of mitral cells, thereby modulating their firing activities. In the rat olfactory bulb, for example, orexin A causes some mitral cells to depolarize and others to hyperpolarize (Apelbaum et al., 2005; Hardy et al., 2005). Thus, if GnRH modulates the olfactory bulbar neural circuit via similar pathway, it may be capable of enhancing sensitivity for certain odorants that are critical for the animal to detect at that time.

Second, it is possible that GnRH modulates the activity of reciprocal synapses between mitral and granule cells. In fact, neuropeptide Y (NPY) alters the efficiency of synapse transmission in the rat olfactory bulb by reducing the amplitude of calcium currents in mitral cells, thereby reducing the probability of glutamate release. Transmission at the excitatory synapses from mitral cells to granule cells is thus inhibited (Blakemore et al., 2006), which could result in a decrease in odorant contrast in the olfactory bulb. GnRH has been shown to affect synaptic transmission in other regions of the nervous system: for example, in the optic tectum of rainbow trout, GnRH modulates the efficiency of synaptic transmission between retinal fibers and periventricular neurons (Kinoshita et al., 2007). In this study, the excitatory postsynaptic currents that are activated by ionotropic glutamate receptors were enhanced by application of GnRH. If GnRH has similar effects in the olfactory bulb, it could affect odorant discrimination or other aspects of olfactory information processing.

We should also consider the possibility that GnRH may act on olfactory bulbar circuits via other neuromodulatory systems. For example, the action of GnRH on retinal neural circuits is mediated by dopaminergic neurons. In teleost retinas, TN-GnRH neurons make synapses on dopaminergic interplexiform cells (Zucker and Dowling, 1987). Application of GnRH causes horizontal cells to depolarize and enhances their responses to small spots while also diminishing responses to full-field light (Umino and Dowling, 1991). The effects of GnRH on horizontal cells are similar to those of dopamine, and are blocked by the application of haloperidol, a dopamine antagonist (Umino and Dowling, 1991). These results indicate that GnRH acts on horizontal cells indirectly, by stimulating the release of dopamine from interplexiform cells. The olfactory bulb also contains dopaminergic interneurons, and the activity of the olfactory bulbar circuits are affected by the application of dopamine (Duchamp-Viret et al., 1997; Hsia et al., 1999; Wachowiak and Cohen, 1999; Ennis et al., 2001; Davison et al., 2004). In rats and box turtles (*Terrapene carolina*), for example, dopamine mediates presynaptic inhibition of olfactory receptor neurons by reducing calcium influx via D2 receptors (Hsia et al., 1999; Wachowiak and Cohen, 1999; Ennis et al., 2001). In northern leopard frogs (*Lithobates* [*Rana*] *pipiens*), dopamine similarly affects the firing activity of mitral cells and inhibits synapse transmission from mitral cells to granule cells (Duchamp-Viret et al., 1997; Davison et al., 2004). Thus, dopamine is broadly involved in the processing of odorant information. If GnRH acts on the dopaminergic interneurons in the olfactory bulb, it could indirectly affect the responsiveness of olfactory bulbar neural circuits as it does in the retina.

Role of GnRH in the olfactory bulb

We have discussed the presence of GnRH-immunoreactive fibers and receptors in the olfactory bulb, as well as the possible modulatory effects of GnRH in the olfactory bulb. What is the functional role of GnRH in the olfactory bulb? If GnRH is released in the olfactory bulb in a physiologically adaptive manner, this question is closely associated with the question of when the concentration of GnRH in the olfactory bulb changes.

Electrophysiological recordings from single TN-GnRH neurons in dwarf gouramis reveal that the majority of these neurons show regular pacemaker activities (Oka and Matsushima, 1993; Abe and Oka, 2007). Furthermore, GnRH release is evoked by a high-potassium depolarizing stimulus that increases the firing frequency of TN-GnRH neurons (Ishizaki et al., 2004). The firing frequencies of TN-GnRH neurons should determine the concentration of GnRH

in the regions they innervate, and the activity of neurons that express GnRH receptors should be regulated by this concentration (Abe and Oka, 2007).

The multimodal sensory inputs to the terminal nerve should affect the release of GnRH into the olfactory bulbar neural circuits. Interestingly, some reports indicate that GnRH concentration in the olfactory bulb does change depending on sensory input. For example, one hour after female prairie voles are exposed to male urine, the GnRH concentration in the posterior olfactory bulb is significantly elevated (Dluzen et al., 1981). Furthermore, the GnRH concentration in the olfactory bulb is also elevated when male mice are exposed not only to the ovariectomized females but also to other males (Dluzen and Ramirez, 1983). Similarly, when a male goldfish is exposed to a female that displays spawning behavior, GnRH concentrations in the olfactory bulb are significantly elevated 1–2 hrs after the exposure (Yu and Peter, 1990). In addition, this increase in GnRH concentration is abolished when the medial olfactory tract, which carries information on female sex pheromones (Stacey and Kyle, 1983), is cut in males (Yu and Peter, 1990). In contrast, when males are exposed to other males, no increase in GnRH concentration occurs. The alteration of GnRH concentrations in the male olfactory bulb could be induced either by pheromonal activation of the GnRH neurons or behavioral interactions with a female fish. Overall, these studies suggest that conspecific chemical signals could affect the activity of neurons in the olfactory bulb via GnRH release.

Furthermore, GnRH concentrations in the olfactory bulb may be related to the physiological condition of the animal. In female Indian major carp, GnRH immunoreactivity in the olfactory bulb changes seasonally, with the density of GnRH-immunoreactive fibers peaking during the prespawning season (Biju et al., 2003). In chum salmon (*Oncorhynchus keta*), GnRH gene expression in the olfactory bulb is elevated when prespawning salmon migrate upstream (Onuma et al., 2005). These lines of evidence strongly suggest that the function of GnRH in the olfactory bulb may be closely associated with the reproductive status of the fish.

DISCUSSION

How does the effect of GnRH vary seasonally?

The concentration of GnRH in the olfactory system changes in accordance with reproductive state in some species. Perhaps seasonal changes in hormone levels or sensory inputs act on TN-GnRH cells so that the amount of GnRH peptide in the olfactory system is increased, regulating olfactory responsiveness in concert with the physiological condition of the animal. However, it is possible that over the course of the breeding season, the expression of GnRH receptors changes in addition to or instead of changes in the amount of GnRH itself. As described above, the modulatory effect of GnRH on the voltage-activated currents in olfactory receptor neurons changes seasonally (Eisthen et al., 2000; Zhang and Delay, 2007). Perhaps this result is due not to changes in the availability of the endogenous ligand, but to changes in the expression or function of GnRH receptors. In European sea bass and masu salmon, it has been reported that the expression level of GnRH receptors in the brain increases or decreases with the transition of seasons (Gonzalez-Martinez et al., 2004; Jodo et al., 2005). Additionally, alternative splice variants of GnRH receptors may be also involved in the control of the sensitivity of neurons to GnRH: in the bullfrog brain, four types of splice variants are generated from the primary transcript of bf GnRHR-3, a subtype of GnRH receptor, and these splice variants inhibit wild-type GnRH receptor-mediated signaling (Wang et al., 2001). Furthermore, the expression levels of the splice variants vary seasonally in many regions of the brain (Wang et al., 2001). Thus, it is possible to control the consequences of GnRH receptor binding by regulating the splicing process of the GnRH receptor primary transcript seasonally.

What is the function of GnRH in the olfactory system?

Because the concentration of GnRH in the olfactory system is related to reproductive state, it seems logical to surmise that the function of GnRH in the olfactory system is to modulate the processing of olfactory information that is important for reproduction. The simplest hypothesis is that GnRH modulates activity in the olfactory system such that the animal can detect chemical cues from prospective partners efficiently, promoting sexual behavior. Nevertheless, it is also possible that GnRH is involved in other interactions with conspecifics (Dluzen et al., 1981; Dluzen and Ramirez, 1983). For example, the modulatory effect of GnRH on the olfactory system may enhance detection of chemosignals from any conspecific animal, facilitating interactions that could be important for reproduction.

Interestingly, in axolotls GnRH suppresses odorant responses elicited by feeding cues (Park and Eisthen, 2003). Perhaps in this context GnRH acts to inhibit feeding behavior so that the salamanders can instead apply their energies to sexual behavior; at the same time, GnRH may also enhance processing of sex pheromones. Such a scenario would explain the observation that GnRH fibers are distributed widely throughout the olfactory bulb, not simply in areas involved in processing odorant cues directly related to sexual behavior (Kim et al., 1995).

We should also consider the possibility that GnRH simply enhances odorant contrast for many categories of odorants in the olfactory system. The TN-GnRH system has been suggested to affect the motivational or arousal state of the animal (Oka and Matsushima, 1993; Yamamoto et al., 1997; Abe and Oka, 2007). If GnRH enhances odorant contrast in general, a motivated animal can respond more appropriately to the external environment. In this case, it is possible that the close relationship between GnRH concentration in the olfactory system and reproductive state may simply reflect motivational state. For example, GnRH gene expression in the olfactory bulb of chum salmon is elevated when they are highly motivated to migrate upriver (Onuma et al., 2005). During this time, it is important for salmon to discriminate the chemical characteristics of rivers via their olfactory system so that they can home precisely to the natal habitat (Dittman and Quinn, 1996). If GnRH enhances odorant contrast in the olfactory system, it would facilitate homing to the natal habitat.

Overall, the TN-GnRH system receives sensory inputs from the somatosensory, visual, and olfactory systems, and such modalities are thought to influence the activity of the neurons involved. Furthermore, some hormones (thyroid hormone, testosterone) are involved in the regulation of GnRH gene expression in the TN-GnRH system in tilapia

(*Oreochromis niloticus*) (Soga et al., 1998; Parhar et al., 2000). Therefore, the release of GnRH from the TN-GnRH system into the olfactory system would be influenced by changes in environmental factors or physiological status, and thus the olfactory responsiveness of the animal would be regulated.

ACKNOWLEDGMENTS

We thank Naoyuki Yamamoto for advice, and Shinji Kanda for help in drawing Fig. 1A. This project was supported in part by grants from NSF (IOS 0817785) and the BRCP program at NIH (R01DC 005366) to H.L.E., and by Grants-in-Aid from the Japan Society for the Promotion of Science (20247005), and the Ministry of Education, Culture, Sports, Science and Technology (20021012) to Y.O.

REFERENCES

Abe H, Oka Y (2007) Neuromodulatory functions of terminal nerve-GnRH neurons. In "Fish Physiology" Ed by TJ Hara, B Zielenski, Elsevier, San Diego, pp 455–503

Adrian ED (1950) The electrical activity of the mammalian olfactory bulb. Electroencephalogr Clin Neurophysiol 2: 377–388

Albertson AJ, Navratil A, Mignot M, Dufourny L, Cherrington B, Skinner DC (2008) Immunoreactive GnRH type I receptors in the mouse and sheep brain. J Chem Neuroanat 35: 326–333

Amano M, Oka Y, Aida K, Okumoto N, Kawashima S, Hasegawa Y (1991) Immunocytochemical demonstration of salmon GnRH and chicken GnRH-II in the brain of masu salmon, *Oncorhynchus masou*. J Comp Neurol 314: 587–597

Amano M, Oka Y, Kitamura S, Ikuta K, Aida K (1998) Ontogenic development of salmon GnRH and chicken GnRH-II systems in the brain of masu salmon (*Oncorhynchus masou*). Cell Tissue Res 293: 427–434

Amano M, Oka Y, Yamanome T, Okuzawa K, Yamamori K (2002) Three GnRH systems in the brain and pituitary of a pleuronectiform fish, the barfin flounder *Verasper moseri*. Cell Tissue Res 309: 323–329

Amano M, Okubo K, Yamanome T, Oka Y, Kawaguchi N, Aida K, Yamamori K (2004) Ontogenic development of three GnRH systems in the brain of a pleuronectiform fish, barfin flounder. Zool Sci 21: 311–317

Apelbaum AF, Perrut A, Chaput M (2005) Orexin A effects on the olfactory bulb spontaneous activity and odor responsiveness in freely breathing rats. Regul Pept 129: 49–61

Arechiga C, Alcocer H (1969) Adrenergic effects on the electro-olfactogram. Exp Med Surg 27: 384–394

Baly C, Aioun J, Badonnel K, Lacroix MC, Durieux D, Schlegel C, Salesse R, Caillol M (2007) Leptin and its receptors are present in the rat olfactory mucosa and modulated by the nutritional status. Brain Res 1129: 130–141

Batten TF, Cambre ML, Moons L, Vandesande F (1990) Comparative distribution of neuropeptide-immunoreactive systems in the brain of the green molly, *Poecilia latipinna*. J Comp Neurol 302: 893–919

Biju KC, Singru PS, Schreibman MP, Subhedar N (2003) Reproduction phase-related expression of GnRH-like immunoreactivity in the olfactory receptor neurons, their projections to the olfactory bulb and in the nervus terminalis in the female Indian major carp *Cirrhinus mrigala* (Ham.). Gen Comp Endocrinol 133: 358–367

Biju KC, Gaikwad A, Sarkar S, Schreibman MP, Subhedar N (2005) Ontogeny of GnRH-like immunoreactive neuronal systems in the forebrain of the Indian major carp, *Cirrhinus mrigala*. Gen Comp Endocrinol 141: 161–171

Blakemore LJ, Levenson CW, Trombley PQ (2006) Neuropeptide Y modulates excitatory synaptic transmission in the olfactory bulb. Neuroscience 138: 663–674

Bouvet J-F, Delaleu J-C, Holley A (1987a) Does the trigeminal nerve control the activity of the olfactory receptor cells? Ann NY Acad Sci 510: 187–189

Bouvet JF, Delaleu JC, Holley A (1987b) Olfactory receptor cell function is affected by trigeminal nerve activity. Neurosci Lett 77: 181–186

Bouvet JF, Delaleu JC, Holley A (1988) The activity of olfactory receptor cells is affected by acetylcholine and substance P. Neurosci Res 5: 214–223

Buck LB (2000) The molecular architecture of odor and pheromone sensing in mammals. Cell 100: 611–618

Caillol M, Aioun J, Baly C, Persuy MA, Salesse R (2003) Localization of orexins and their receptors in the rat olfactory system: possible modulation of olfactory perception by a neuropeptide synthetized centrally or locally. Brain Res 960: 48–61

Cao Y, Oh BC, Stryer L (1998) Cloning and localization of two multigene receptor families in goldfish olfactory epithelium. Proc Natl Acad Sci USA 95: 11987–11992

Chartrel N, Bruzzone F, Leprince J, Tollemer H, Anouar Y, Do-Rego JC, Segalas-Milazzo I, Guilhaudis L, Cosette P, Jouenne T, et al. (2006) Structure and functions of the novel hypothalamic RFamide neuropeptides R-RFa and 26RFa in vertebrates. Peptides 27: 1110–1120

Chess A, Simon I, Cedar H, Axel R (1994) Allelic inactivation regulates olfactory receptor gene expression. Cell 78: 823–834

Chiba A (1997) Distribution of neuropeptide Y-like immunoreactivity in the brain of the bichir, Polypterus senegalus, with special regard to the terminal nerve. Cell Tissue Res 289: 275–284

Chiba A (2000) Immunohistochemical cell types in the terminal nerve ganglion of the cloudy dogfish, *Scyliorhinus torazame*, with special regard to neuropeptide Y/FMRFamide-immunoreactive cells. Neurosci Lett 286: 195–198

Chiba A (2005) Neuropeptide Y-immunoreactive (NPY-ir) structures in the brain of the gar *Lepisosteus oculatus* (Lepisosteiformes, Osteichthyes) with special regard to their anatomical relations to gonadotropin-releasing hormone (GnRH)-ir structures in the hypothalamus and the terminal nerve. Gen Comp Endocrinol 142: 336–346

Chiba A, Sohn YC, Honma Y (1996) Immunohistochemical and ultrastructural characterization of the terminal nerve ganglion cells of the ayu, *Plecoglossus altivelis* (Salmoniformes, Teleostei). Anat Rec 246: 549–556

Christopher Kirk E, Smith DW (2003) Protection from acoustic trauma is not a primary function of the medial olivocochlear efferent system. J Assoc Res Otolaryngol 4: 445–465

Czesnik D, Schild D, Kuduz J, Manzini I (2007) Cannabinoid action in the olfactory epithelium. Proc Natl Acad Sci USA 104: 2967–2972

D'Aniello B, Pinelli C, Di Fiore MM, Tela L, King JA, Rastogi RK (1995) Development and distribution of gonadotropin-releasing hormone neuronal systems in the frog (*Rana esculenta*) brain: immunohistochemical analysis. Brain Res Dev Brain Res 89: 281–288

Date-Ito A, Ohara H, Ichikawa M, Mori Y, Hagino-Yamagishi K (2008) Xenopus V1R vomeronasal receptor family is expressed in the main olfactory system. Chem Senses 33: 339–346

Davison IG, Boyd JD, Delaney KR (2004) Dopamine inhibits mitral/tufted→granule cell synapses in the frog olfactory bulb. J Neurosci 24: 8057–8067

Dittman A, Quinn T (1996) Homing in Pacific salmon: mechanisms and ecological basis. J Exp Biol 199: 83–91

Dluzen DE, Ramirez VD (1983) Localized and discrete changes in neuropeptide (LHRH and TRH) and neurotransmitter (NE and DA) concentrations within the olfactory bulbs of male mice as a function of social interaction. Horm Behav 17: 139–145

Dluzen DE, Ramirez VD, Carter CS, Getz LL (1981) Male vole urine changes luteinizing hormone-releasing hormone and norepi-

nephrine in female olfactory bulb. Science 212: 573–575
Dockray GJ (2004) The expanding family of -RFamide peptides and their effects on feeding behaviour. Exp Physiol 89: 229–235
Duchamp-Viret P, Coronas V, Delaleu JC, Moyse E, Duchamp A (1997) Dopaminergic modulation of mitral cell activity in the frog olfactory bulb: a combined radioligand binding-electrophysiological study. Neuroscience 79: 203–216
Dumalska I, Wu M, Morozova E, Liu R, van den Pol A, Alreja M (2008) Excitatory effects of the puberty-initiating peptide kisspeptin and group I metabotropic glutamate receptor agonists differentiate two distinct subpopulations of gonadotropin-releasing hormone neurons. J Neurosci 28: 8003–8013
Eisthen HL (2004) The goldfish knows: olfactory receptor cell morphology predicts receptor gene expression. J Comp Neurol 477: 341–346
Eisthen HL, Polese G (2006) Evolution of vertebrate olfactory subsystems. In "Evolution of Nervous Systems, Vol 2, Non-Mammalian Vertebrates" Ed by J Kaas, Academic Press, Oxford, UK, pp 355–406
Eisthen HL, Delay RJ, Wirsig-Wiechmann CR, Dionne VE (2000) Neuromodulatory effects of gonadotropin releasing hormone on olfactory receptor neurons. J Neurosci 20: 3947–3955
Ennis M, Zhou FM, Ciombor KJ, Aroniadou-Anderjaska V, Hayar A, Borrelli E, Zimmer LA, Margolis F, Shipley MT (2001) Dopamine D2 receptor-mediated presynaptic inhibition of olfactory nerve terminals. J Neurophysiol 86: 2986–2997
Firestein S (2001) How the olfactory system makes sense of scents. Nature 413: 211–218
Fischer AJ, Reisch HM, Kyle AL, Stell WK (1996) Characterization of the RFamide-like neuropeptides in the nervus terminalis of the goldfish (*Carassius auratus*). Regul Peptides 62: 73–87
Friedrich RW, Korsching SI (1997) Combinatorial and chemotopic odorant coding in the zebrafish olfactory bulb visualized by optical imaging. Neuron 18: 737–752
Friedrich RW, Laurent G (2001) Dynamic optimization of odor representations by slow temporal patterning of mitral cell activity. Science 291: 889–894
Friedrich RW, Habermann CJ, Laurent G (2004) Multiplexing using synchrony in the zebrafish olfactory bulb. Nat Neurosci 7: 862–871
Fritsch G (1878) Untersuchungen über den feineren Bau des Fischgehirns mit besonderer Berücksichtigung der Homologien bei anderen Wirbelthierklassen. Gutmann'schen Buchhandlung, Berlin
Fujimoto M, Takeshita K, Wang X, Takabatake I, Fujisawa Y, Teranishi H, Ohtani M, Muneoka Y, Ohta S (1998) Isolation and characterization of a novel bioactive peptide, *Carassius* RFamide (C-RFa), from the brain of the Japanese crucian carp. Biochem Biophys Res Commun 242: 436–440
Fuller CL, Yettaw HK, Byrd CA (2006) Mitral cells in the olfactory bulb of adult zebrafish (*Danio rerio*): morphology and distribution. J Comp Neurol 499: 218–230
Getchell TV, Kwong K, Saunders CP, Stromberg AJ, Getchell ML (2006) Leptin regulates olfactory-mediated behavior in ob/ob mice. Physiol Behav 87: 848–856
Gonzalez-Martinez D, Madigou T, Zmora N, Anglade I, Zanuy S, Zohar Y, Elizur A, Munoz-Cueto JA, Kah O (2001) Differential expression of three different prepro-GnRH (gonadotrophin-releasing hormone) messengers in the brain of the european sea bass (*Dicentrarchus labrax*). J Comp Neurol 429: 144–155
Gonzalez-Martinez D, Zmora N, Mananos E, Saligaut D, Zanuy S, Zohar Y, Elizur A, Kah O, Munoz-Cueto JA (2002) Immunohistochemical localization of three different prepro-GnRHs in the brain and pituitary of the European sea bass (*Dicentrarchus labrax*) using antibodies to the corresponding GnRH-associated peptides. J Comp Neurol 446: 95–113
Gonzalez-Martinez D, Madigou T, Mananos E, Cerda-Reverter JM, Zanuy S, Kah O, Munoz-Cueto JA (2004) Cloning and expression of gonadotropin-releasing hormone receptor in the brain and pituitary of the European sea bass: an in situ hybridization study. Biol Reprod 70: 1380–1391
Grens KE, Greenwood AK, Fernald RD (2005) Two visual processing pathways are targeted by gonadotropin-releasing hormone in the retina. Brain Behav Evol 66: 1–9
Hanson LR, Sorensen PW, Cohen Y (1998) Sex pheromones and amino acids evoke distinctly different spatial patterns of electrical activity in the goldfish olfactory bulb. Ann NY Acad Sci 855: 521–524
Hardy AB, Aioun J, Baly C, Julliard KA, Caillol M, Salesse R, Duchamp-Viret P (2005) Orexin A modulates mitral cell activity in the rat olfactory bulb: patch-clamp study on slices and immunocytochemical localization of orexin receptors. Endocrinology 146: 4042–4053
Hasegawa T, Satoh M, Ueda K (1994) Intracellular study of generation mechanisms of induced wave in carp (*Cyprinus carpio*) olfactory bulb. Comp Biochem Physiol A 108: 17–23
Hegg CC, Lucero MT (2004) Dopamine reduces odor- and elevated-K(+)-induced calcium responses in mouse olfactory receptor neurons in situ. J Neurophysiol 91: 1492–1499
Hegg CC, Greenwood D, Huang W, Han P, Lucero MT (2003) Activation of purinergic receptor subtypes modulates odor sensitivity. J Neurosci 23: 8291–8301
Hilal EM, Chen JH, Silverman AJ (1996) Joint migration of gonadotropin-releasing hormone (GnRH) and neuropeptide Y (NPY) neurons from olfactory placode to central nervous system. J Neurobiol 31: 487–502
Hsia AY, Vincent JD, Lledo PM (1999) Dopamine depresses synaptic inputs into the olfactory bulb. J Neurophysiol 82: 1082–1085
Illing N, Troskie BE, Nahorniak CS, Hapgood JP, Peter RE, Millar RP (1999) Two gonadotropin-releasing hormone receptor subtypes with distinct ligand selectivity and differential distribution in brain and pituitary in the goldfish (*Carassius auratus*). Proc Natl Acad Sci USA 96: 2526–2531
Ishizaki M, Iigo M, Yamamoto N, Oka Y (2004) Different modes of gonadotropin-releasing hormone (GnRH) release from multiple GnRH systems as revealed by radioimmunoassay using brain slices of a teleost, the dwarf gourami (*Colisa lalia*). Endocrinology 145: 2092–2103
Jodo A, Kitahashi T, Taniyama S, Bhandari RK, Ueda H, Urano A, Ando H (2005) Seasonal variation in the expression of five subtypes of gonadotropin-releasing hormone receptor genes in the brain of masu salmon from immaturity to spawning. Zool Sci 22: 1331–1338
Karunadasa DK, Chapman C, Bicknell RJ (2006) Expression of pheromone receptor gene families during olfactory development in the mouse: expression of a V1 receptor in the main olfactory epithelium. Eur J Neurosci 23: 2563–2572
Kashiwadani H, Sasaki YF, Uchida N, Mori K (1999) Synchronized oscillatory discharges of mitral/tufted cells with different molecular receptive ranges in the rabbit olfactory bulb. J Neurophysiol 82: 1786–1792
Kawai F, Kurahashi T, Kaneko A (1999) Adrenaline enhances odorant contrast by modulating signal encoding in olfactory receptor cells. Nat Neurosci 2: 133–138
Kawano T, Margolis F (1985) Catecholamines in olfactory mucosa decline following superior cervical ganglionectomy. Chem Senses 10: 353–356
Kim KH, Patel L, Tobet SA, King JC, Rubin BS, Stopa EG (1999) Gonadotropin-releasing hormone immunoreactivity in the adult and fetal human olfactory system. Brain Res 826: 220–229
Kim MH, Oka Y, Amano M, Kobayashi M, Okuzawa K, Hasegawa Y, Kawashima S, Suzuki Y, Aida K (1995) Immunocytochemical localization of sGnRH and cGnRH-II in the brain of goldfish, *Carassius auratus*. J Comp Neurol 356: 72–82

Kinoshita M, Kobayashi S, Urano A, Ito E (2007) Neuromodulatory effects of gonadotropin-releasing hormone on retinotectal synaptic transmission in the optic tectum of rainbow trout. Eur J Neurosci 25: 480–484

Laurent G, Stopfer M, Friedrich RW, Rabinovich MI, Volkovskii A, Abarbanel HD (2001) Odor encoding as an active, dynamical process: experiments, computation, and theory. Annu Rev Neurosci 24: 263–297

Liberles SD, Buck LB (2006) A second class of chemosensory receptors in the olfactory epithelium. Nature 442: 645–650

Locy WA (1905) On a newly recognized nerve connected with the fore-brain of selachians. Anat Anzeiger 26: 111–123

Lucero MT, Squires A (1998) Catecholamine concentrations in rat nasal mucus are modulated by trigeminal stimulation of the nasal cavity. Brain Res 807: 234–236

Maison S, Micheyl C, Collet L (2001) Influence of focused auditory attention on cochlear activity in humans. Psychophysiology 38: 35–40

Manley GA (2000) Cochlear mechanisms from a phylogenetic viewpoint. Proc Natl Acad Sci USA 97: 11736–11743

Manley GA (2001) Evidence for an active process and a cochlear amplifier in nonmammals. J Neurophysiol 86: 541–549

Michel MC (2004) Neuropeptide Y and Related Peptides. Springer, Berlin

Mombaerts P, Wang F, Dulac C, Chao SK, Nemes A, Mendelsohn M, Edmondson J, Axel R (1996) Visualizing an olfactory sensory map. Cell 87: 675–686

Montefusco-Siegmund RA, Romero A, Kausel G, Muller M, Fujimoto M, Figueroa J (2006) Cloning of the prepro C-RFa gene and brain localization of the active peptide in *Salmo salar*. Cell Tissue Res 325: 277–285

Mousley A, Polese G, Marks NJ, Eisthen HL (2006) Terminal nerve-derived neuropeptide Y modulates physiological responses in the olfactory epithelium of hungry axolotls (*Ambystoma mexicanum*). J Neurosci 26: 7707–7717

Naito T, Saito Y, Yamamoto J, Nozaki Y, Tomura K, Hazama M, Nakanishi S, Brenner S (1998) Putative pheromone receptors related to the Ca^{2+}-sensing receptor in *Fugu*. Proc Natl Acad Sci USA 95: 5178–5181

Ngai J, Chess A, Dowling MM, Necles N, Macagno ER, Axel R (1993) Coding of olfactory information: topography of odorant receptor expression in the catfish olfactory epithelium. Cell 72: 667–680

Ni MM, Luo Y, Liu J, Liao DQ, Tang YD (2008) FMRFamide modulates outward potassium currents in mouse olfactory sensory neurons. Clin Exp Pharmacol Physiol 35: 563–567

Nobili R, Mammano F, Ashmore J (1998) How well do we understand the cochlea? Trends Neurosci 21: 159–167

Oka Y (1997) The gonadotropin-releasing hormone (GnRH) neuronal system of fish brain as a model system for the study of peptidergic neuromodulation. In "GnRH Neurons: Genes to Behavior" Ed by IS Parhar, Y Sakuma, Brain Shuppan Publishers, Tokyo, pp 245–276

Oka Y, Ichikawa M (1990) Gonadotropin-releasing hormone (GnRH) immunoreactive system in the brain of the dwarf gourami (*Colisa lalia*) as revealed by light microscopic immunocytochemistry using a monoclonal antibody to common amino acid sequence of GnRH. J Comp Neurol 300: 511–522

Oka Y, Matsushima T (1993) Gonadotropin-releasing hormone (GnRH)-immunoreactive terminal nerve cells have intrinsic rhythmicity and project widely in the brain. J Neurosci 13: 2161–2176

Okubo K, Nagahama Y (2008) Structural and functional evolution of gonadotropin-releasing hormone in vertebrates. Acta Physiol (Oxf) 193: 3–15

Okubo K, Sakai F, Lau EL, Yoshizaki G, Takeuchi Y, Naruse K, Aida K, Nagahama Y (2006) Forebrain gonadotropin-releasing hormone neuronal development: insights from transgenic medaka and the relevance to X-linked Kallmann syndrome. Endocrinology 147: 1076–1084

Onuma T, Higa M, Ando H, Ban M, Urano A (2005) Elevation of gene expression for salmon gonadotropin-releasing hormone in discrete brain loci of prespawning chum salmon during upstream migration. J Neurobiol 63: 126–145

Pager J (1978) Ascending olfactory information and centrifugal influxes contributing to a nutritional modulation of the rat mitral cell responses. Brain Res 140: 251–269

Pager J, Giachetti I, Holley A, Le Magnen J (1972) A selective control of olfactory bulb electrical activity in relation to food deprivation and satiety in rats. Physiol Behav 9: 573–579

Parhar IS, Soga T, Sakuma Y (2000) Thyroid hormone and estrogen regulate brain region-specific messenger ribonucleic acids encoding three gonadotropin-releasing hormone genes in sexually immature male fish, *Oreochromis niloticus*. Endocrinology 141: 1618–1626

Park D, Eisthen HL (2003) Gonadotropin releasing hormone (GnRH) modulates odorant responses in the peripheral olfactory system of axolotls. J Neurophysiol 90: 731–738

Park D, Zawacki SR, Eisthen HL (2003) Olfactory signal modulation by molluscan cardioexcitatory tetrapeptide (FMRFamide) in axolotls (*Ambystoma mexicanum*). Chem Senses 28: 339–348

Peter RE, Prasada Rao PD, Baby SM, Illing N, Millar RP (2003) Differential brain distribution of gonadotropin-releasing hormone receptors in the goldfish. Gen Comp Endocrinol 132: 399–408

Propper CR, Moore FL (1991) Effects of courtship on brain gonadotropin hormone-releasing hormone and plasma steroid concentrations in a female amphibian (*Taricha granulosa*). Gen Comp Endocrinol 81: 304–312

Puel JL, Bonfils P, Pujol R (1988) Selective attention modifies the active micromechanical properties of the cochlea. Brain Res 447: 380–383

Rajan R (2000) Centrifugal pathways protect hearing sensitivity at the cochlea in noisy environments that exacerbate the damage induced by loud sound. J Neurosci 20: 6684–6693

Rall W, Shepherd GM (1968) Theoretical reconstruction of field potentials and dendrodendritic synaptic interactions in olfactory bulb. J Neurophysiol 31: 884–915

Rodriguez I, Greer CA, Mok MY, Mombaerts P (2000) A putative pheromone receptor gene expressed in human olfactory mucosa. Nat Genet 26: 18–19

Saraiva LR, Korsching SI (2007) A novel olfactory receptor gene family in teleost fish. Genome Res 17: 1448–1457

Satake H, Minakata H, Wang X, Fujimoto M (1999) Characterization of a cDNA encoding a precursor of *Carassius* RFamide, structurally related to a mammalian prolactin-releasing peptide. FEBS Lett 446: 247–250

Sato Y, Miyasaka N, Yoshihara Y (2007) Hierarchical regulation of odorant receptor gene choice and subsequent axonal projection of olfactory sensory neurons in zebrafish. J Neurosci 27: 1606–1615

Sawada K, Ukena K, Satake H, Iwakoshi E, Minakata H, Tsutsui K (2002) Novel fish hypothalamic neuropeptide. Eur J Biochem 269: 6000–6008

Schild D, Restrepo D (1998) Transduction mechanisms in vertebrate olfactory receptor cells. Physiol Rev 78: 429–466

Schoppa NE (2006) Synchronization of olfactory bulb mitral cells by precisely timed inhibitory inputs. Neuron 49: 271–283

Schwanzel-Fukuda M, Pfaff DW (1989) Origin of luteinizing hormone-releasing hormone neurons. Nature 338: 161–164

Schwanzel-Fukuda M, Morrell JI, Pfaff DW (1985) Ontogenesis of neurons producing luteinizing hormone-releasing hormone (LHRH) in the nervus terminalis of the rat. J Comp Neurol 238: 348–364

Schwanzel-Fukuda M, Morrell JI, Pfaff DW (1986) Localization of

choline acetyltransferase and vasoactive intestinal polypeptide-like immunoreactivity in the nervus terminalis of the fetal and neonatal rat. Peptides 7: 899–906
Scott JW, Scott-Johnson PE (2002) The electroolfactogram: a review of its history and uses. Microsc Res Tech 58: 152–160
Shepherd GM (1994) Discrimination of molecular signals by the olfactory receptor neuron. Neuron 13: 771–790
Shepherd GM (2004) The Synaptic Organization of the Brain. 5 ed, Oxford University Press, Oxford, UK
Shepherd GM, Brayton RK (1979) Computer simulation of a dendro-dendritic synaptic circuit for self- and lateral-inhibition in the olfactory bulb. Brain Res 175: 377–382
Soga T, Sakuma Y, Parhar IS (1998) Testosterone differentially regulates expression of GnRH messenger RNAs in the terminal nerve, preoptic and midbrain of male tilapia. Brain Res Mol Brain Res 60: 13–20
Soga T, Ogawa S, Millar RP, Sakuma Y, Parhar IS (2005) Localization of the three GnRH types and GnRH receptors in the brain of a cichlid fish: insights into their neuroendocrine and neuromodulator functions. J Comp Neurol 487: 28–41
Speca DJ, Lin DM, Sorensen PW, Isacoff EY, Ngai J, Dittman AH (1999) Functional identification of a goldfish odorant receptor. Neuron 23: 487–498
Stacey NE, Kyle AL (1983) Effects of olfactory tract lesions on sexual and feeding behavior in the goldfish. Physiol Behav 30: 621–628
Stopfer M, Bhagavan S, Smith BH, Laurent G (1997) Impaired odour discrimination on desynchronization of odour-encoding neural assemblies. Nature 390: 70–74
Subhedar N, Rama Krishna NS (1988) Immunocytochemical localization of LH-RH in the brain and pituitary of the catfish, *Clarias batrachus* (Linn.). Gen Comp Endocrinol 72: 431–442
Teruyama R, Beck MM (2000) Changes in immunoreactivity to anti-cGnRH-I and -II are associated with photostimulated sexual status in male quail. Cell Tissue Res 300: 413–426
Tsutsui K, Ukena K (2006) Hypothalamic LPXRF-amide peptides in vertebrates: identification, localization and hypophysiotropic activity. Peptides 27: 1121–1129
Umino O, Dowling JE (1991) Dopamine release from interplexiform cells in the retina: effects of GnRH, FMRFamide, bicuculline, and enkephalin on horizontal cell activity. J Neurosci 11: 3034–3046
Vassar R, Ngai J, Axel R (1993) Spatial segregation of odorant receptor expression in the mammalian olfactory epithelium. Cell 74: 309–318
Wachowiak M, Cohen LB (1999) Presynaptic inhibition of primary olfactory afferents mediated by different mechanisms in lobster and turtle. J Neurosci 19: 8808–8817
Wakabayashi Y, Mori Y, Ichikawa M, Yazaki K, Hagino-Yamagishi K (2002) A putative pheromone receptor gene is expressed in two distinct olfactory organs in goats. Chem Senses 27: 207–213
Wakabayashi Y, Ohkura S, Okamura H, Mori Y, Ichikawa M (2007) Expression of a vomeronasal receptor gene (V1r) and G protein alpha subunits in goat, *Capra hircus*, olfactory receptor neurons. J Comp Neurol 503: 371–380
Wang L, Oh DY, Bogerd J, Choi HS, Ahn RS, Seong JY, Kwon HB (2001) Inhibitory activity of alternative splice variants of the bullfrog GnRH receptor-3 on wild-type receptor signaling. Endocrinology 142: 4015–4025
Weeg MS, Land BR, Bass AH (2005) Vocal pathways modulate efferent neurons to the inner ear and lateral line. J Neurosci 25: 5967–5974
Wetzel CH, Spehr M, Hatt H (2001) Phosphorylation of voltage-gated ion channels in rat olfactory receptor neurons. Eur J Neurosci 14: 1056–1064
White J, Meredith M (1995) Nervus terminalis ganglion of the bonnethead shark (*Sphyrna tiburo*): evidence for cholinergic and catecholamingeric influence on two cell types distinguished by peptide immunocytochemistry. J Comp Neurol 351: 385–403
Wirsig CR (1987) Effects of lesions of the terminal nerve on mating behavior in the male hamster. Ann NY Acad Sci 519: 241–251
Wirsig CR, Getchell TV (1986) Amphibian terminal nerve: distribution revealed by LHRH and AChE markers. Brain Res 385: 10–21
Wirsig CR, Leonard CM (1986a) Acetylcholinesterase and luteinizing hormone-releasing hormone distinguish separate populations of terminal nerve neurons. Neuroscience 19: 719–740
Wirsig CR, Leonard CM (1986b) The terminal nerve projects centrally in the hamster. Neuroscience 19: 709–717
Wirsig-Wiechmann CR (1990) The nervus terminalis in the chick: a FMRFamide-immunoreactive and AChE-positive nerve. Brain Res 523: 175–179
Wirsig-Wiechmann CR (1993) Peripheral projections of nervus terminalis LHRH-containing neurons in the tiger salamander, *Ambystoma tigrinum*. Cell Tissue Res 273: 31–40
Wirsig-Wiechmann CR, Ebadifar B (2002) The naris muscles in tiger salamander II. Innervation as revealed by enzyme histochemistry and immunocytochemistry. Anat Embryol 205: 181–186
Wirsig-Wiechmann CR, Jennes L (1993) Gonadotropin-releasing hormone agonist binding in tiger salamander nasal cavity. Neurosci Lett 160: 201–204
Wirsig-Wiechmann CR, Oka Y (2002) The terminal nerve ganglion cells project to the olfactory mucosa in the dwarf gourami. Neurosci Res 44: 337–341
Wirsig-Wiechmann CR, Wiechmann AF (2001) The prairie vole vomeronasal organ is a target for gonadotropin-releasing hormone. Chem Senses 26: 1193–1202
Wirsig-Wiechmann CR, Wiechmann AF, Eisthen HL (2002) What defines the nervus terminalis? Neurochemical, developmental, and anatomical criteria. Prog Brain Res 141: 45–58
Wray S, Grant P, Gainer H (1989) Evidence that cells expressing luteinizing hormone-releasing hormone mRNA in the mouse are derived from progenitor cells in the olfactory placode. Proc Natl Acad Sci USA 86: 8132–8136
Xiao Z, Suga N (2002) Modulation of cochlear hair cells by the auditory cortex in the mustached bat. Nat Neurosci 5: 57–63
Yamamoto N, Ito H (2000) Afferent sources to the ganglion of the terminal nerve in teleosts. J Comp Neurol 428: 355–375
Yamamoto N, Oka Y, Amano M, Aida K, Hasegawa Y, Kawashima S (1995) Multiple gonadotropin-releasing hormone (GnRH)-immunoreactive systems in the brain of the dwarf gourami, *Colisa lalia*: immunohistochemistry and radioimmunoassay. J Comp Neurol 355: 354–368
Yamamoto N, Oka Y, Kawashima S (1997) Lesions of gonadotropin-releasing hormone-immunoreactive terminal nerve cells: effects on the reproductive behavior of male dwarf gouramis. Neuroendocrinology 65: 403–412
Yokoi M, Mori K, Nakanishi S (1995) Refinement of odor molecule tuning by dendrodendritic synaptic inhibition in the olfactory bulb. Proc Natl Acad Sci USA 92: 3371–3375
Yu KL, Peter RE (1990) Alterations in gonadotropin-releasing hormone immunoactivities in discrete brain areas of male goldfish during spawning behavior. Brain Res 512: 89–94
Zhang W, Delay RJ (2007) Gonadotropin-releasing hormone modulates voltage-activated sodium current and odor responses in *Necturus maculosus* olfactory sensory neurons. J Neurosci Res 85: 1656–1667
Zucker CL, Dowling JE (1987) Centrifugal fibres synapse on dopaminergic interplexiform cells in the teleost retina. Nature 330: 166–168

(Received May 14, 2009 / Accepted July 8, 2009)